REMARKS

Reconsideration is respectfully requested in view of the foregoing remarks which follow.

Claims 1-31, 34-45, 55-75 and 79-86 are pending in the application.

Claims 1-31, 34-45, 55-75 and 79-86 stand rejected under 35 USC § 103(a) as being unpatentable over Luo et al. (*Bioconjugate Chem.* 1999) in view of Sparer et al. *Controlled Delivery Systems*, Chapter 6, 1983, Li et al. US 5, 977,163 and Desai et al. US 5,648,506. This rejection is respectfully traversed.

Applicants respectfully submit that in the outstanding Office Action, the Examiner persists in misinterpreting the results of the comparative tests provided by Applicants and in overrating the importance of Luo et al.'s teaching, so that once again the claimed invention has been rejected for obviousness.

Particularly, at page 8 of the Office Action, the Examiner asserts that the arguments submitted by the Applicants are not found to be persuasive for the following reasons:

> "Applicants are pointing out to the results for just one type of cell line (HCT-116 colon cancer cell lines) in Luo and arguing that compared to this particular result their conjugates are superior. Applicants have carried out their tests on human breast adenocarcinoma cells, which are different. Applicants' conjugates have an ester linkage, whereas Luo's conjugates have an amide link. Luo shows results for three different cancer cell lines (SK-OV-3: ovary adenocarcinoma; HBL-100: human breast cancer; HCT-116: colon cancer). Perusal of results shown in Table 3 of Luo shows that the Taxol equivalents are different for different cell lines and different preparations. One of ordinary skill in the art would expect such results and hence would look for other conjugates that are more active than the ones taught by Luo".

Applicants traverse this reasoning and the conclusion derived therefrom by the Examiner. As a matter of fact, at page 761 of Luo et al., second column, second paragraph, reference is made to Figure 7, wherein the cytotoxicity of four different cell lines have been shown. The four different cell lines are:

- SK-OV-3: human ovary adenocarcinoma cell line;

- HBL-100: human breast cancer cell line;

- HCT-116: human colon cancer cell line;

- NIH 3-T-3: mouse embryonic fibroblast cell line.

In the above-mentioned paragraph, Luo et al. describe the results they obtained, wherein it is clear that the best cytotoxicity of HA-ADH-Taxol is against the **human colon cancer cell line HCT-116**. That is why Luo et al. selected that cell line for the further investigation of conjugate behaviour, as shown in Figure 8 and reported in the third paragraph, page 761, second column.

In fact, it is evident that the authors were understandably interested in studying in depth the best results, i.e. against the human colon cancer. **As a consequence, Applicants, wishing to make apparent the unexpected results achieved by the conjugates of the claimed invention, found it appropriate and significant to provide a comparison between the claimed conjugates and the HA-ADH-Taxol of Luo et al. using the same cell line whereon the latter has been most successful.**

As a matter of fact, it has been demonstrated as a result of that comparison that, on HCT-116 cells, the claimed conjugates act notably better than free Taxol, which, in turn, acts better than the only known conjugate, namely, HA-ADH-Taxol preparations, bearing in mind that on HCT-116 cells the latter achieved the best results.

As reported above, the Examiner states that "Perusal of results shown in Table 3 of Luo shows that the Taxol equivalents are different for different cell lines and different

preparations. One of ordinary skill in the art would expect such results and hence would look for other conjugates that are more active than the ones taught by Luo."

Thus, **the Examiner de facto acknowledged the technical problem underlying the current invention**, wherein the unsatisfactory results of the prior art made it strongly desirable to find different and better solutions. It should be also noted that **Luo et al., indeed, teach away** from considering the disclosed conjugate typology as being promising, thus leading the skilled person to divert from the direction of the claimed invention, as already argued in Applicants' previous reply.

Therefore, a person of ordinary skill wishing to solve the technical problem set forth would never have found in Luo et al. any useful indication or guidance, being conversely **prevented from recognizing and appreciating the desirability of conjugates containing both HA and Taxol, since Luo et al. clearly discourage those of ordinary skill in the art from considering them.**

Although the teaching of Luo et al. is a clear teaching away, the Examiner is persuaded that Luo et al. however suggest to try in the direction of the claimed invention, in view of the "notion that increased cytotoxicity of HA-Taxol conjugate requires cellular uptake of the complex followed by hydrolytic release of the active Taxol by cleavage of the labile 2'-ester linkage".

Therefore, in the Examiner's opinion, "one of ordinary skill in the art, based on this teaching of Luo will expect a conjugate of Taxol and HA linked via an ester bond to be more active and hence would look for such conjugates as instantly claimed. One would also look for other types of linkages (based on the teaching of the secondary references, Sparer and Desai) that may be better than the ester linkage suggested by Luo."

The Applicants also emphatically traverse this conclusion, since **irrespective of the mechanism of Taxol release, the conjugate of Luo et el. has proved to act worse than free Taxol**. It means that no matter how the Taxol is released, **the conjugate of Luo et al. is clearly unsatisfactory**. Thus, the Applicants wonder why the person of

ordinary skill "based on this teaching of Luo, will expect a conjugate of Taxol and HA linked via an ester bond to be more active".

In Applicants' view, this is indeed **a further confirmation that Luo et al. teach away from the current invention**, because, even if we suppose hypothetically that the person of ordinary skill had noticed the cleavage of the labile 2'-ester linkage as the Taxol release mechanism in the cell (that follows the cellular uptake), he/she could not possibly ignore the unsatisfactory results obtained. Thus, he/she would have never found it relevant or even promising to know that an ester bond cleaves when releasing Taxol in the cell. In fact, **he/she could, at most, have also ascribed the unsatisfactory results to the presence of the ester bond, thus preventing him/her from further searching in that direction.**

It should be also be kept in mind that even the following Examiner's assertion is incorrect: "the artisan can vary the molecular weight for optimization purposes. According to Luo's teaching (page 761, right column, last paragraph though page 762 right column) cytotoxicity depends on a balance between minimal hyaluronic acid modification and maximal Taxol loading. This is a suggestion for adjustment of the percentage of Taxol loading especially if the molecular weight of hyaluronic acid is increased, i.e., more repeat units are added to the HA chain."

As a matter of fact, the above indicated teaching of Luo et al, indeed recites "high loading decreases the solubility of HA-Taxol conjugate and thus limits the cytotoxicity of the conjugate relative to that of the free drug" (Luo et al, page 762, lines 1-7). Thus, the cytotoxicity decreases as the Taxol loading increases, as already discussed in the previous reply. This comment expressly refers to the tested **preparations 1, 3, 7 and 8** and to the results reported as shown in Table 3. However, Table 2 teaches that:

$(HA)_x(HA\text{-}ADH)_y(HA\text{-}ADH\text{-}Taxol)_z$

preparation	composition of HA–Taxol conjugates: HA (x) (%)	HA-ADH (y) (%)	HA-ADH-Taxol (z) (%)	solubility in H_2O	ADH%: Taxol-NHS[a]
		A. ADH loading = 9%[b]			
→1	91	7.8	1.2	yes	9:5
2	91	7.7	1.3	yes	9:9
→3	91	3.8	5.2	yes	9:18
		B. ADH loading = 18%			
4	82	16.4	1.6	yes	18:5
5	82	16.1	1.9	yes	18:10
6	82	15.8	2.2	yes	18:15
→7	82	3.1	14.9	partially[c]	18:36
		C. ADH loading = 45%			
→8	55	30	15	no	45:90

It is clear from Table 2 that **all the tested preparations do not involve at all the conjugate HA-ADH-Taxol as such, but indeed compositions having different % amounts of HA, HA-ADH and HA-ADH-Taxol**. This means that Luo et al. is led to affirm that "cytotoxicity depends on a balance between minimal hyaluronic acid modification and maximal Taxol loading", on the basis of the ADH loading of HA-ADH (ADH modification) and the Taxol loading as ADH%:Taxol-NHS, while commenting on the behaviour observed for **preparations of precursors and final product**.

The Examiner deems the above conclusions of Luo et al. which expressly refer to preparations as being directly and equivalently valid also for the conjugates of the claimed invention, notwithstanding the fact that the conjugates are specific and distinct compounds and clearly not compositions. However, at the time the invention was made, the skilled person would ***never have misinterpreted the prior art*** as has been done by the Examiner, whose knowledge is derived solely from the claimed invention. This ***ex post facto* analysis** is not admissible since it is a clear case of **hindsight reconstruction**.

Indeed, the skilled person would only know from Luo et al. that the sole conjugate disclosed therein is definitely undesirable with regard to many aspects:

- the **conjugate** of Luo et al. **as such** is **fivefold less effective** than the free Taxol as such, when directly compared to each other (ratio free Taxol/conjugate = **0.21 times**);

- the HA must have low molecular weights, otherwise the effectiveness disadvantageously decreases;

- the preparations tested show the necessity of a balance between minimal hyaluronic acid modification and maximal Taxol loading, since otherwise the resulting product loses cytotoxicity and solubility, as reported in Table 2 of Luo et al.

Therefore, the person having ordinary skill, having knowledge that a result of **fivefold less effective** than the free Taxol is the best possible result for Luo et al.'s conjugate, since **any change that may be supposed is already addressed as involving a worse case result**, would not derive any benefit from noticing the Taxol release mechanism, since the results concerned on all the tested cells are, in any event, ***unsatisfactory***.

Therefore, the skilled person would have **never found** in **Luo et al.** any useful suggestion. Instead, he would be led conversely to divert his investigations away from the claimed invention.

The Examiner further asserts that "the skilled person can take the suggestion in the secondary references and apply them to Luo's teaching for modification purposes." However, as already discussed in the previous reply:

- Sparer et al. concern glycosaminoglycans drug complexes, i.e. cysteine-GAG and chloramphenicol-GAG complexes. This document, not only does not address HA as such, but also, as is well-recognized even by the Examiner, never cites Taxol.

- Li et al. refer to paclitaxel and docetaxel complexes with polyethylene glycol polymers.

- Desai et al. refer to Taxol complexes with polyethylene glycols, similar to Li et al.

In view of the above, Applicants wonder how the skilled person could possibly deem said secondary references to be relevant, at the time the subject invention was made, when all the conjugates disclosed therein are expressly different and no suggestion at all can be recognized to search in the direction of the claimed invention.

Also, in this case, the Examiner came to his/her conclusions by an **ex post facto analysis**, i.e. by a **hindsight reconstruction** having knowledge of the invention. Indeed, **there is no motivation whatsoever to combine the teaching of the cited documents**.

However, even if hypothetically combined, the skilled person would, at most, have disregarded any consideration of conjugates involving HA for releasing Taxol in cancer cells, since Luo et al. had results which were unsatisfactory, and none of the secondary references is able to remedy these deficiencies in the teachings of Luo et al., since none of them discloses, concerns or even cites Taxol.

For all the above reasons, Applicants are convinced that the conjugates as set forth in Claim 1 and all of the dependent claims are unobvious over the prior art documents when taken in combination. Since the preponderance of the evidence clearly establishes that the claims distinguish over the combination of art advanced by the Examiner, the § 103(a) rejection has been overcome and should be withdrawn since the Examiner has failed to support a case of *prima facie* obviousness. Applicants have convincingly demonstrated that their claimed conjugates represent an advance over the prior art and, as such, the issuance of a Notice of Allowance is deserved and solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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